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A Randomized Trial of the Effects of Early Cardiac Serum Marker Availability on Reperfusion Therapy in Patients With Acute Myocardial Infarction

The Serial Markers, Acute Myocardial Infarction and Rapid Treatment Trial (SMARTT)

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OBJECTIVES The purpose of this study was to assess whether the immediate availability of serum markers would increase the appropriate use of thrombolytic therapy.

BACKGROUND Serum markers such as myoglobin and creatine kinase, MB fraction (CK-MB) are effective in detecting acute myocardial infarction (AMI) in the emergency setting. Appropriate candidates for thrombolytic therapy are not always identified in the emergency department (ED), as 20% to 30% of eligible patients go untreated, representing 10% to 15% of all patients with AMI. Patients presenting with chest pain consistent with acute coronary syndrome were evaluated in the EDs of 12 hospitals throughout North America.

METHODS In this randomized, controlled clinical trial, physicians received either the immediate myoglobin/CK-MB results at 0 and 1 h after enrollment (stat) or conventional reporting of myoglobin/CK-MB 3 h or more after hospital admission (control). The primary end point was the comparison of the proportion of patients within the stat group versus control group who received appropriate thrombolytic therapy. Secondary end points included the emergent use of any reperfusion treatment in both groups, initial hospital disposition of patients (coronary care unit, monitor or nonmonitor beds) and the proportion of patients appropriately discharged from the ED.

RESULTS Of 6,352 patients enrolled, 814 (12.8%) were diagnosed as having AMI. For patients having AMI, there were no statistically significant differences in the proportion of patients treated with thrombolytic therapy between the stat and control groups (15.1% vs. 17.1%, $p = 0.45$). When only patients with ST segment elevation on their initial electrocardiogram were compared, there were still no significant differences between the groups. Also, there was no difference in the hospital placement of patients in critical care and non–critical care beds. The availability of early markers was associated with more hospital admissions as compared to the control group, as the number of patients discharged from the ED was decreased in the stat versus control groups (28.4% vs. 31.5%, $p = 0.023$).

CONCLUSIONS The availability of 0- and 1-h myoglobin and CK-MB results after ED evaluation had no effect on the use of thrombolytic therapy for patients presenting with AMI, and it slightly increased the number of patients admitted to the hospital who had no evidence of acute myocardial necrosis. (J Am Coll Cardiol 2000;36:1500–6) © 2000 by the American College of Cardiology

It has been unequivocally demonstrated that thrombolytic therapy improves survival in patients with ST segment elevation acute myocardial infarction (AMI) (1–3). The proportion of patients treated, however, is less than what would be projected from both clinical trial and registry data (4–7). For example, electrocardiographic (ECG) findings from 6,000 consecutive patients with AMI admitted to the hospital who were included in the Myocardial Infarction, Triage and Intervention Project indicated that ST segment elevation or new bundle branch block was evident in >50% of patients on the initial ECG (4–6). Yet, thrombolytic therapy was prescribed to only 25% to 30% of these patients (6,7). Retrospective assessment of patient eligibility for therapy consistently suggested that up to 10% to 25% more of these patients were appropriate candidates for treatments (6,7). The reasons for this discrepancy are unclear.

Arrival to the hospital after 12 h, contraindications to thrombolytic therapy, older age and atypical or resolving symptoms account for many, but not all, decisions to withhold treatment. Failure to initially recognize ST segment elevations on the 12-lead ECG or misunderstanding of the significance of lesser levels of chest pain can also lead to underutilization of therapy. In one study, 20% of appar-

*See the Appendix for a listing of all of the investigators' affiliations. This study was presented in part at the meeting of the American College of Cardiology, March 1997, Anaheim, California, and was supported in part by an unrestricted grant from Genentech, Inc., South San Francisco, California and Dade Stratus, Inc., Miami, Florida.

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Abbreviations and Acronyms

AMI	=	acute myocardial infarction
CCU	=	coronary care unit
CK-MB	=	creatine kinase, MB fraction
ECG	=	electrocardiogram
ED	=	emergency department
EMCREG	=	Emergency Medicine Cardiac Research Group
LBBB	=	left bundle branch block
PTCA	=	percutaneous coronary transluminal angioplasty
SMARTT	=	Serial Markers, Acute Myocardial Infarction and Rapid Treatment Trial
stat	=	immediate (0 and 1 h myoglobin/CK-MB)

ently eligible patients who were <75 years of age and presented to the hospital within 6 h did not receive thrombolytic therapy (8). In another study, 16% of all patients with ST segment elevation infarcts were not initially recognized (9).

Serial testing for the early serum markers of myocardial necrosis, myoglobin and creatine kinase, MB fraction (CK-MB) is an effective method for identifying patients with AMI (10–13). Myoglobin levels are elevated in over two-thirds of patients with AMI at the time of presentation to the emergency department (ED) and are present in the serum of virtually all within 6 h after symptom onset (10). Elevated levels of CK-MB are present in ~40% of patients on initial hospital presentation. This proportion increases to >90% of patients with AMI having positive CK-MB levels by 6 h after ED presentation (11,13). The routine use of sensitive serum markers of myocardial necrosis in the very early period after presentation to the ED may provide an incremental aid for identifying patients with evolving AMI, particularly in those with less obvious symptoms and less profound ECG abnormalities.

In the Serial Markers, Acute Myocardial Infarction and Rapid Treatment Trial (SMARTT), we assessed the impact of using immediate (0 and 1 h) serial myoglobin and CK-MB determinations (stat) on the use of thrombolytic therapy in patients with AMI in the emergency setting. Our hypothesis was that the availability of serial early cardiac serum markers would lead to a 25% relative increase in the proportion of patients receiving appropriate thrombolytic therapy in the ED. We also sought to determine whether such testing would influence the rate of coronary care unit (CCU) admission and direct discharge from the ED.

METHODS

Setting. The SMARTT study was a multicenter, prospective, randomized, controlled clinical trial conducted in 12 academic, community and military hospitals in the United States and Canada with active emergency centers (see Appendix). Patients were randomized using a central telephone system, and data were collected and analyzed at a central coordinating center in Seattle, Washington. The ECG data were centrally read in a blinded fashion at the Ischemia Monitoring Core Laboratory, Duke Clinical Research Institute, Durham, North Carolina, and serum samples were sent to a core laboratory at the University of Cincinnati for quality assurance testing and determination of myoglobin and CK-MB in the control group.

Protocol design. The SMARTT study included a prospective, observational pilot phase analyzing the sensitivity and specificity of the serum markers in a chest pain population (14). In this pilot study, an optimal early serum marker sensitivity rate of 70.8% was determined at 0 and 1 h after hospital presentation for myoglobin or CK-MB. The pilot trial was then followed by a prospective, randomized trial in which half of the patients at each center had "stat" testing results reported within the first 3 h, whereas in the "control" group, blood was drawn but testing or reporting was delayed until at least 3 h or more.

Patients were eligible for enrollment in the study if they presented to the ED of the participating hospitals with chest pain consistent with a possible acute coronary syndrome. All participants were able to give informed consent. Exclusions for the study were age <25 years, altered mental status, pregnancy or inability or unwillingness to have a follow-up evaluation. Patients whose chest pain was obviously noncardiac, on the basis of history, physical examination or X-ray findings, were also excluded, as were patients with ST segment elevation treated with reperfusion at the time of the initial evaluation. Thus, the target group included those patients whose treating physician was uncertain as to the cause of chest pain. All patients included in the trial had ECGs performed as part of their initial ED evaluation.

After informed consent was provided, blood was drawn, which was transported to the site laboratory under special identification. The laboratory technician then called a central telephone randomization center that provided the allocation assignment. Control samples were frozen and shipped to the core laboratory for quality assurance of site readings. Positive cardiac serum markers were defined as levels >100 ng/ml for myoglobin and >6 ng/ml for CK-MB. The ECG readings were also independently verified. ST segment elevation was defined as >1 mV in two contiguous limb leads or >2 mV in two contiguous anterior leads. Routine baseline, 6- to 8-h and 12- to 18-h CK and CK-MB results were obtained for all patients admitted to the hospital. "Acute myocardial infarction" was defined by World Health Organization criteria as elevation of CK-MB in a characteristic pattern, as measured by serial blood samples, or the evolution of ECG changes after presentation in patients with chest pain. Patients were treated according to the standard of care at each institution. In the stat marker assessment group, the results of the 0- and 1-h CK-MB and myoglobin testing were made available to the treating emergency physician immediately, allowing clinical decisions to be made with the results at hand. In the control

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group, the results of any cardiac serum marker testing were withheld by the laboratory for ≥3 h before being released.

Patients were followed during their stay in the ED and subsequent hospital stay to determine the outcome. In addition to the primary diagnosis, the date and time of discharge to home or admission to the hospital were ascertained, as well as the type of hospital ward (CCU, unmonitored bed or monitored non-CCU bed) for admitted patients. Admitted patients were followed to determine their final diagnosis (International Classification of Diseases, 9th Revision), with AMI confirmed by cardiac marker elevation and ECG changes. Any in-patient cardiovascular complications were also documented. The date and time of thrombolytic therapy, coronary angiography, coronary angioplasty or coronary artery bypass graft procedures were also recorded. Patients discharged directly from the ED were contacted at 7 to 14 days by telephone or letter. Any subsequent readmissions, myocardial infarctions or deaths were documented.

Outcome measures. The primary end point was the proportion of patients treated with thrombolytic therapy within 3 h of ED presentation. Secondary end points included the use of any emergent reperfusion treatment, including thrombolytic therapy or primary percutaneous transluminal coronary angioplasty (PTCA), within 3 h of hospital presentation, the percentage of patients who received treatment and who did not meet ECG criteria (ST segment elevation or new bundle branch block) on their initial ECG in the ED and initial patient disposition from the ED, including the proportion of patients discharged home or admitted to non-CCU beds.

Sample size and statistical analysis. The sample size for the randomized trial was calculated to detect a 25% relative increase in thrombolytic therapy utilization in the subset of patients with AMI determined by standard cardiac enzyme testing at each medical center (>2 times elevation in CK or CK-MB in any of the 0- to 16-h samples) or characteristic ECG changes. The sample size necessary to detect this difference (alpha = 0.05, beta = 0.2) was 815 patients with AMI per group. We estimated from retrospective data that enrollment of a total of 7,000 patients would generate 1,630 patients with AMI. A Data and Safety Monitoring Board analyzed the data at predefined interim points.

The stat and control groups were compared using a two-tailed chi-square test; $p < 0.05$ was considered significant. When there were significant differences between the stat and control groups at baseline, analyses were performed after adjustment using the Mantel-Haensel test. All statistical analyses were carried out using the SAS statistical package. The study was approved by each medical center's Human Subjects Review Committee.

RESULTS

Of the 6,388 patients enrolled in the randomized trial, 36 were excluded because of insufficient data (Fig. 1). Most of these lacked in-hospital serum marker data sufficient to be assigned to AMI versus non-AMI groups by protocol definition. None received reperfusion treatment. Of the patients who were discharged from the ED, follow-up was obtained in 96.4%. The trial was discontinued before enrolling the target sample size when it became apparent that there were no trends toward significant differences in the primary outcome between the stat and control groups.

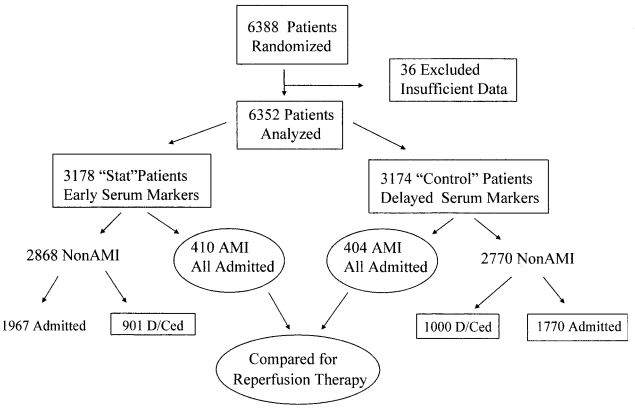

Figure 1. Patient flow and follow-up diagram. (Discharged = D/Ced)

Of the 6,352 patients with complete data evaluated in this trial, 3,178 were randomized to the stat group and 3,174 were randomized to the control group. Of these, 1,901 patients (29.9%) were discharged home from the ED, whereas 4,451 were admitted to the hospital. For the trial, 814 patients (12.7%) had enzyme evidence of AMI per protocol: 410 in the stat group and 404 in the control group.

Patient demographic data. Baseline characteristics for patients enrolled in SMARTT are summarized in Table 1. Patients with AMI proved to be older than those without AMI (64 years old [25%, 75% = 55 years old, 74 years old] vs. 59 years old [25%, 75% = 48 years old, 71 years old] [$p = 0.0006$]) and were more likely to be male ($p = 0.001$), have a history of myocardial infarction ($p = 0.003$), have diabetes ($p = 0.006$) and have a history of hypercholesterolemia ($p = 0.016$). A greater number of patients with AMI were current smokers ($p = 0.003$).

The median time to ED presentation from symptom onset in patients with and without AMI is shown in Table 1. There was a statistically significant difference in time to arrival between the stat and control groups in patients with AMI ($p = 0.0014$), but not in patients without AMI ($p = 0.34$). For patients with AMI, hospital arrival to treatment with thrombolytic therapy was nearly identical: 2.9 h (25%, 75% = 0.7 h, 1.9 h) for stat patients versus 2.5 h (25%, 75% = 0.6 h, 1.4 h) for control subjects. The discharge diagnoses for the two groups are listed in Figure 2. There were no significant differences in the percentages of patients in each group with AMI, unstable angina, stable angina or unspecified chest pain. In the 814 patients subsequently diagnosed with AMI, the initial ECG findings are shown in Figure 3. There were no significant differences between the two

Table 1. Baseline Characteristics: Randomized Trial

	Non-AMI		AMI		
	Stat* (n = 2,768)	Control (n = 2,770)	Stat (n = 410)	Control (n = 404)	p Value†
Mean age (yrs)	59.9	59.1	63.4	64	0.0006
Gender (% male)	56	56	66	70	0.001
Medical histories (%)					
Hypertension	54	54	54	56	NS
Previous MI	32	30	37	36	0.003
Congestive heart failure	14	15	16	15	NS
Coronary artery bypass graft surgery	15	16	14	14	NS
Percutaneous transluminal coronary angioplasty	19	18	13	18	NS
Diabetes	21	22	27	25	0.006
Hypercholesterolemia	26	26	31	29	0.016
Current smoking	27	27	34	30	0.003
Time from symptom onset to ED arrival in median hours (25%, 75% percentiles)	3 (1.4, 6.0)	2.8 (1.3, 6.2)	2.2‡ (1.1, 5.9)	2.7 (1.2, 7.2)	NS

*There were no significant differences between the stat and control groups for all variables in the non-AMI and AMI groups. †Non-AMI vs. AMI. ‡In patients with AMI, the difference in time from symptom onset to arrival at the hospital in stat vs. control groups (p = 0.0014).

AMI = acute myocardial infarction; ED = emergency department; MI = myocardial infarction; NS = not significant; stat = immediate (0 and 1 h) serial myoglobin and creatine kinase, MB fraction determinations.

groups in the percentages of patients with ST segment elevation, left bundle branch block (LBBB) or new Q waves.

Serum marker results. Serum enzyme results for the patients in the randomized trial are shown in Table 2. Of the 6,352 patients in the trial, 16.7% had positive myoglobin results and 9.6% had positive CK-MB results at 0 or 1 h after ED presentation. Of the patients randomized to the stat group, 19.2% had positive CK-MB or myoglobin studies in the ED, compared with 19.3% in the control group (p = 0.905). Of the 814 patients who were diagnosed with myocardial infarction, 64.1% had positive myoglobin studies in the ED at either 0 or 1 h after presentation (sensitivity 64.1%, specificity 90.2%), 52.6% had positive CK-MB studies at either 0 or 1 h (sensitivity 52.6%, specificity 96.7%) and 72% had either positive CK-MB or myoglobin at 0 or 1 h after presentation (sensitivity 72%, specificity 88.5%). Of patients diagnosed with AMI, 69% in the stat group had positive cardiac serum markers in the ED, compared with 75% in the control group (p = 0.06).

Reperfusion therapy. For the primary end point in SMARTT, the proportion of all patients with AMI treated with thrombolytic agents in the stat group within 3 h after randomization was 15.1%, as compared with 17.1% in the control group, which had serum marker results delayed for ≥3 h (p = 0.45). Of the patients in the stat group, 21.7% received either thrombolytic therapy or primary PTCA within 3 h of randomization, compared with 24.5% in the control group (p = 0.34).

When the subset of patients with ST segment elevation and AMI were analyzed, there remained no differences between the groups in the use of thrombolytic therapy alone (39.5% for stat vs. 42.1% for control; p = 0.70) or with thrombolysis or PTCA (58.5% for stat vs. 64.2% for control; p = 0.42). Likewise, when patients with LBBB on the presenting ECG were analyzed, there were no differences in thrombolytic therapy or PTCA utilization between the groups, either when AMI was subsequently diagnosed or when it was not.

Of 2,868 patients diagnosed *without* AMI, six patients (0.2%) in the stat group and 10 (0.36%) of 2,770 patients in the control group received thrombolytic therapy or PTCA within 3 h of randomization (p = NS). No adverse outcomes were observed. Looking more closely at the effects of positive cardiac markers in the ED, we analyzed the rate of thrombolytic therapy utilization in patients with positive serum markers and either ST segment elevation or nonspecific ECG findings on their initial ECG in the ED. In

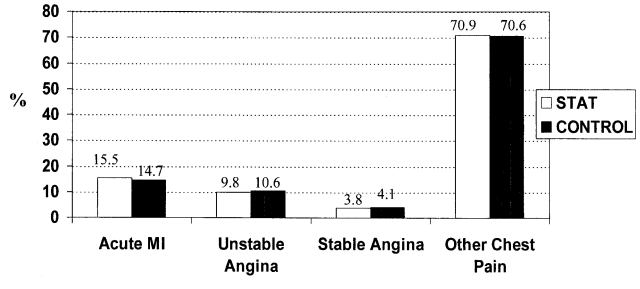

Figure 2. Discharge diagnoses: All trial patients, comparing stat versus control groups. P = NS for all comparisons.

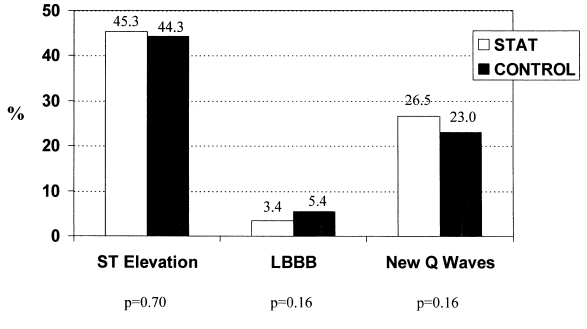

Figure 3. Electrocardiographic findings in all patients with AMI, comparing stat versus control groups.

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Table 2. Sensitivity and Specificity of Serum Markers for Acute Myocardial Infarction*

Marker	Sensitivity (%)	Specificity (%)
Myoglobin	64.1	90.2
CK-MB	52.6	96.7
Either myoglobin or CK-MB	72	88.5

*Sensitivity and specificity of markers at either 0 or 1 h after arrival at the emergency department.
CK-MB = creatine kinase, MB fraction.

patients with ST segment elevation and positive cardiac serum markers in the ED, 44.2% in the stat group received thrombolytic therapy within 3 h, compared with 44.6% in the control group ($p = 0.993$). In patients without ST segment elevation, but with positive cardiac serum markers in the ED, no patient in either group was treated with thrombolytic therapy or primary PTCA within 3 h. To determine whether positive cardiac serum markers in the ED resulted in inappropriate treatment of patients without AMI, we analyzed thrombolytic therapy use in patients with positive cardiac serum markers in the ED who were subsequently not diagnosed with AMI (false positive cardiac serum markers in the ED). In these patients, 0.76% in the stat group were treated with thrombolytics within 3 h, compared with 0.43% in the control group ($p = 0.641$).

Hospital disposition. Discharge rates and hospital utilization are indicated for the two groups in Figure 4. There were no significant differences between the groups in the distribution of admissions to the CCU, monitored or nonmonitored beds. A total of 1,901 patients (29.8%) were discharged home from the ED. In the stat group, 901 (28.4%) of 3,178 patients and 1,000 (31.5%) of 3,174 patients in the control group were released. This difference was statistically significant ($p = 0.023$). There was no difference in the length of hospital stay between the stat and control groups for patients with or without AMI.

DISCUSSION

Early detection of AMI. Over the past decade, multiple studies have examined the sensitivity and specificity of several early serum markers for detecting myocardial necrosis in the emergency setting. New technology has made it possible to have stat testing and reporting of these serum markers in <1 h after a blood sample is obtained, allowing for "real-time" decision-making in the ED. To date, no study has been done to determine whether this information affects initial clinical decision-making regarding reperfusion therapy. Myoglobin (molecular weight [mw] 17,000 daltons) and CK-MB (mw 82,000 daltons), in particular, have emerged as effective early markers of myocardial necrosis (10–15). One large study suggests that early elevation of these markers indicates greater risk of ischemic complications for the patient (16).

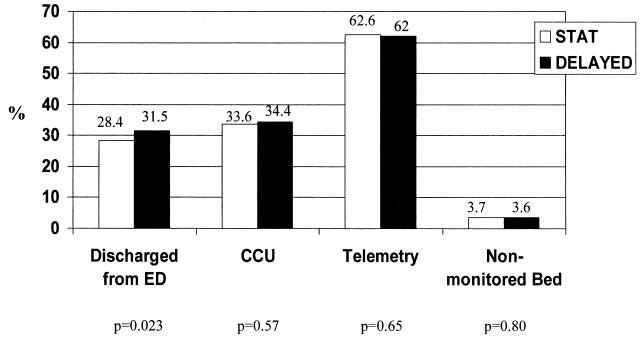

Figure 4. Hospital disposition: all trial patients, comparing stat versus control groups.

Treatment decisions. Serum markers of myocardial necrosis, typically analyzed retrospectively in most studies, have not been extensively evaluated for a real-time impact on physician decision-making in the ED. Two studies conducted by the Emergency Medicine Cardiac Research Group (EMCREG) demonstrated that emergency physicians would use stat serum CK-MB levels in their evaluation of patients with a nondiagnostic ECG and a possible acute coronary syndrome presenting to the ED (17,18). The EMCREG-3 study evaluated the potential utility of 0- and 3-h serum markers in 1,042 patients presenting to the ED with nondiagnostic ECGs. Using 0- and 3-h sampling, elevated CK-MB levels resulted in statistically significant increases in the disposition of patients from the ED to a CCU, whereas negative CK-MB levels tended to influence emergency physicians to admit these patients to a less intensive care setting of the hospital. An important finding was that a negative CK-MB level did not result in the inappropriate discharge of patients with unstable angina to home (18).

This study was designed to clarify the impact of having CK-MB and myoglobin results available on the initial clinical decision-making. It is important to emphasize that all EDs participating in this trial were staffed by Board-eligible/Board-certified emergency physicians with extensive experience in evaluating patients with chest pain and treating AMI. In the U.S., elevated cardiac serum markers are not typically used, without typical ST segment elevation, to identify candidates for treatment with thrombolytic therapy. By providing rapid availability of myoglobin and CK-MB to the emergency physician, we anticipated that elevated levels would potentially increase awareness of an evolving AMI and stimulate appropriate administration of a fibrinolytic agent to these patients.

In this trial, myoglobin and CK-MB levels drawn at 0 and 1 h and made available to the clinician did not increase the proportion of patients with AMI, with or without ST segment elevation, receiving thrombolytic therapy or primary PTCA. Patients with LBBB, a nonspecific indicator of patients who will benefit from thrombolytic therapy, also did not have increased administration of thrombolytic therapy in the ED. Even when only patients with positive cardiac markers in the ED were analyzed, there was no increase in reperfusion therapy noted in patients whose serum marker results were available to the treating ED clinician. Importantly, the availability of "stat" serum mark-

ers did not increase the inappropriate use of thrombolytic therapy in patients without ST segment elevation or in patients who were subsequently not diagnosed with AMI.

Disposition decisions. The results of two previous studies of resource utilization were not confirmed in this trial (17,18). No difference in CCU admissions was observed for either group. A statistically significant difference was seen, however, in the discharge of patients to home from the ED (28.4% in the stat group vs. 31.5% in the control group). Contact with patients discharged from the ED within the first two weeks, or subsequent review of their medical records over longer periods, did not reveal excessive ischemic complications in the stat versus control group.

Study limitations. The lack of impact of 0- and 1-h myoglobin and CK-MB levels on physician decision-making in the emergency setting in SMARTT may be due to several factors. Elevation of a sensitive but nonspecific indicator of myocardial necrosis, such as serum myoglobin, may not be a sufficient stimulus for the physician to increase surveillance for ST segment elevation on the initial 12-lead ECG. A positive myoglobin in the first hour, combined with a negative CK-MB level in this period, may actually have had a negative influence on physician behavior. Negative serum levels of CK-MB, a relatively specific indicator of myocardial necrosis, may have influenced the decision not to start treatment, as the elevation of myoglobin may have been considered falsely positive. Zero- and 1-h determinations of myoglobin and CK-MB were chosen from the pilot trial to maximize the earliest possible time to treatment with thrombolytic therapy, rather than to maximize diagnostic capability. Studies suggest the optimal diagnostic window for myoglobin and CK-MB is 0 and 3 h, so the full impact of these serum markers on physician decision-making, especially resource allocation, may not have been realized by our trial (10–13,19–24). In addition, patients with AMI in the stat group presented earlier (2.2 h) than those in the control group (2.7 h). It would be expected, owing to release kinetics of the serum markers myoglobin and CK-MB, that patients with AMI in the stat group would therefore be less likely to have early cardiac serum marker elevation influencing the decision of the clinician to administer thrombolytic therapy. This is also supported by the finding that 69% of the stat group had positive cardiac serum markers in the ED, compared with 75% in the control group, whose members arrived at the ED later.

The magnitude of the impact of a negative or positive CK-MB level on resource utilization (CCU, monitored, nonmonitored beds) may not be realized owing to our study design. By contrast, the role of serum markers in helping to identify patients who can be safely discharged from the ED appears to be substantiated by this study. Clinicians understanding the release kinetics of these serum markers, and thus expecting negative cardiac serum marker results in this very early period, may have felt more comfortable discharging patients after a negative clinical evaluation and negative cardiac serum markers over a 3-h period and a nondiagnostic 12-lead ECG, rather than basing their decision to discharge the patient from the ED on "stat" serum marker data available in 1 h. Further study is necessary to evaluate the impact of early cardiac serum markers on clinical decision-making in the emergency setting, perhaps with blood samples timed to maximize diagnostic accuracy or trials exploring more specific cardiac markers such as troponin T or I (25–29).

APPENDIX

Investigators and Study Sites for SMARTT

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